

Approach to esophageal absent contractility: can we do better?

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Abstract

Absent contractility (AC), a motility disorder characterized by the absence of esophageal contractions while maintaining normal lower esophageal sphincter relaxation, is recognized as a distinctive major disorder of peristalsis on esophageal high-resolution manometry that warrants comprehensive understanding. This unique motility disorder often co-occurs with connective tissue, rheumatologic or autoimmune diseases, with scleroderma being the classic example. Symptoms of gastroesophageal reflux are common. AC can profoundly impact patients' lives and result in a spectrum of complications, including erosive esophagitis, esophageal candidiasis, Barrett's esophagus, and malnutrition. To address the intricate complexities of AC and its multifaceted complications, a multidisciplinary approach is paramount. This approach considers the distinct clinical presentation and underlying rheumatologic conditions of the individual patient, recognizing the inherent diversity within this disorder. While medical management of gastroesophageal reflux remains the cornerstone of AC treatment, emerging surgical and endoscopic interventions offer additional therapeutic options for those grappling with this challenging condition. This comprehensive review provides an in-depth evaluation of recent advances in our understanding of AC and its management. It endeavors to offer valuable insights into therapeutic strategies for AC and its associated issues.

Keywords Absent contractility, esophageal motility disorders, gastroesophageal reflux disease, diagnosis, management

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Introduction

Absent contractility (AC) is considered a major motility disorder according to the Chicago classification and is defined as a total absence of esophageal contractions, along with normal relaxation of the lower esophageal sphincter (LES) and normal integrated relaxation pressure (Fig. 1) [1,2]. The diagnosis of AC is based on high-resolution manometry (HRM) findings.

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Type I achalasia is a different disorder that also features absent esophageal contractility and can thus mimic AC [2]. While type I achalasia has impaired relaxation of the LES to distinguish it from AC, these 2 distinct esophageal conditions may share common clinical presentations and manometric findings. Adjunctive tests, such as barium swallow and EndoFLIP, may be helpful in determining the proper diagnosis when HRM is borderline [2]. Patients with AC also frequently have a loss of peristaltic reserve when undergoing multiple rapid swallows during HRM [3].

AC is associated with other diseases and conditions. While AC may be idiopathic, it can also be seen along with: connective tissue, rheumatologic or autoimmune diseases, such as scleroderma; neuromuscular disorders, such as multiple sclerosis and muscular dystrophy; type 1 diabetes mellitus; after radiation therapy; long-segment Barrett's esophagus or severe reflux esophagitis (Los Angeles grade D); medications, such as steroids, opiates, anticholinergics and immunosuppressants; after infections, such as polio, Chagas, infectious mononucleosis and human immunodeficiency virus; and after surgical procedures, such as Heller myotomy or peroral endoscopic myotomy (POEM) [4] (Table 1).

Notably, AC is the common manometric pattern after POEM, particularly for type I achalasia [5].

Patients with AC often suffer from gastroesophageal reflux disease (GERD). Importantly, erosive esophagitis (EE) is a common finding in AC and has been reported in up to 65% of scleroderma patients with AC and concomitant esophageal symptoms [6]. Because of the potential reflux symptoms, severe EE, esophageal stricture, esophageal candidiasis, Barrett's esophagus, aspiration, esophageal cancer, and malnutrition, AC can be a debilitating lifelong condition that negatively impacts quality of life [6,7]. In the current review, we aim to present the most current therapeutic approaches for AC and its complications, with a focus on GERD management, nutritional support, and the potential role of endoscopic/surgical interventions.

Prevalence of AC in different populations

AC is a rare disorder and its prevalence has been assessed in several populations. In a recent study of healthy volunteers, AC was diagnosed in just 2 of 469 studies, giving a prevalence of 0.4% [8]. In studies of patients with non-obstructive dysphagia undergoing esophageal HRM, AC is found in 3.6-7.1% [9,10]. In a study of over a thousand GERD patients being evaluated for anti-reflux surgery, 3.2% were found to have "esophageal aperistalsis", a name often used before the term AC was coined [11].

AC is known to be more frequently found in patients with connective tissue, rheumatologic, or autoimmune diseases such as scleroderma (systemic sclerosis), sarcoidosis, amyloidosis, systemic lupus erythematosus, and rheumatoid arthritis. Of these, it is most commonly seen in scleroderma, with numerous studies showing a prevalence of AC in scleroderma ranging from 50-80% [12-20]. Notably, scleroderma commonly affects the gastrointestinal tract, where the esophagus is the most common involved organ, leading to dysphagia, reflux symptoms, and potentially lung complications due to aspirations [4,21-23]. Scleroderma leads to esophageal smooth muscle atrophy and extensive esophageal fibrosis, resulting in esophageal dysmotility and producing symptoms of dysphagia, heartburn, regurgitations, chest pain, feeding difficulties, and weight loss [13,24]. A study by Carlson *et al* that combined HRM and FLIP panometry measurements in patients with

scleroderma found heterogeneous patterns of primary and secondary esophageal peristalsis [20].

AC and rheumatologic diseases

Several studies have evaluated the prevalence of rheumatologic diseases in patients with AC. The first study was by Laique *et al* [4], who evaluated 207 patients with AC. They found that 63% had systemic sclerosis, and an additional 18% were found to have another rheumatologic disease. Subsequent studies from Spain (43.1%) [25], Japan (40.7%) [26], the United States (37.3%) [27], and Israel (21.6%) [28] confirmed that a significant percentage of AC patients have an underlying rheumatologic or autoimmune disease. In contrast, in a study from Vietnam, none of the 204 patients with AC had any rheumatologic disease [29]. These findings are summarized in Table 2.

Some of these differences in the rates of rheumatologic disease may be due to how the rheumatologic or systemic autoimmune diseases were defined, and which diagnoses were included, as this has not been standardized in the literature. Additionally, the populations being evaluated are likely to have played a major role. From these studies, it appears that the study by Dao *et al* is an outlier, given its lack of any rheumatologic diseases [29], but so is the study by Laique *et al*, with its extremely high rate [4]. Thus, it appears that the true percentage of AC patients with an underlying rheumatologic disease is likely to be in the 21-43% range seen in most of the other studies, and not >80% as was found in the Laique *et al* study. Their high rate of rheumatologic disease may be explained by referral bias, as it appears that a high percentage of rheumatology patients underwent manometric evaluation because of the close coordination between the rheumatology and gastroenterology divisions at their medical center.

Finally, the study of Cohen *et al* improved our knowledge of the natural history of AC [28]. With a mean follow up of 20.5 months for the study's AC patients, they found that none of the AC patients without a rheumatologic disease at the time of diagnosis developed one during follow up. Accordingly, they concluded that an evaluation for rheumatologic diseases in a patient with newly-diagnosed AC is probably unnecessary.

Treatment of GERD symptoms and EE in patients with AC

The mainstay of GERD treatment in patients with AC is proton-pump inhibitors (PPIs), but the standard recommended dose, its long-term efficacy, and the need for combination therapy are all issues requiring further elucidation [13]. No specific study of AC patients is available in the literature. Hendel *et al* showed good efficacy of omeprazole to control GERD symptoms in scleroderma patients and to reduce EE severity. However, complete healing of EE was not achieved in half of the cases, as the reflux continued along

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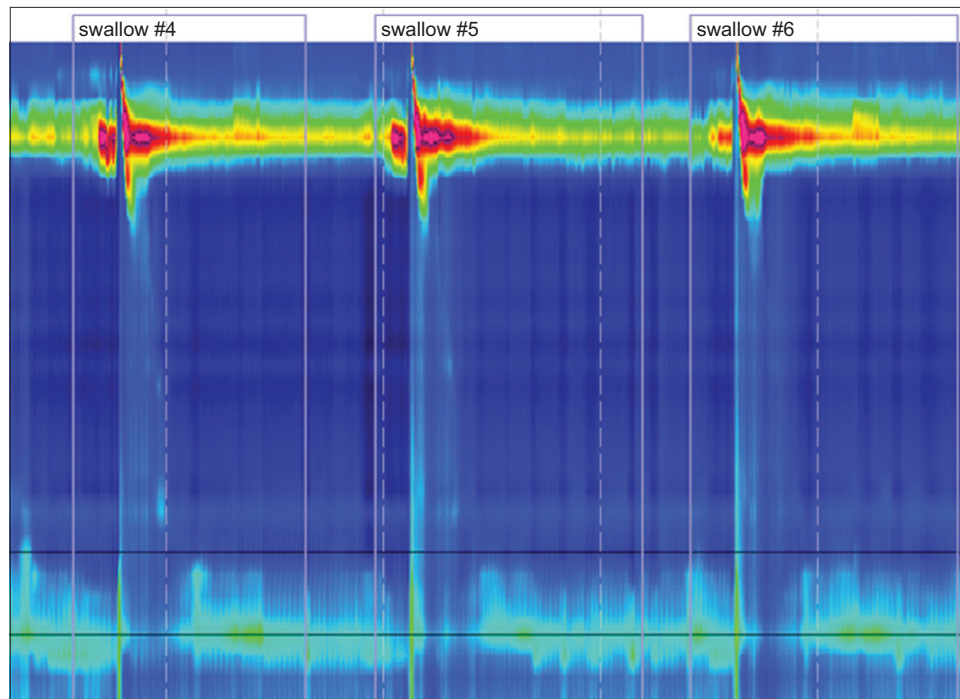


Figure 1 Typical high-resolution manometry findings in a patient with Absent Contractility. In this image, 3 swallows are shown. With each swallow, no contractility is noted in the esophageal body while appropriate relaxation of the lower esophageal sphincter is clearly seen

Table 1 Causes of esophageal absent contractility

Causes	
Rheumatological/ Autoimmune disease	Systemic sclerosis (scleroderma)
	Sarcoidosis
	Amyloidosis
	Arthritis
	Systemic lupus erythematosus
Neuromuscular disorders	Myopathic disorder
	Multiple sclerosis
Metabolic	Muscular dystrophy
	Type 1 diabetes mellitus
Localized inflammatory/ fibrotic diseases	Long-segment Barrett's esophagus
	Severe reflux esophagitis
Medications	Post-radiation therapy
	Steroids
	Opiates
	Anticholinergics
Post-infectious	Immunosuppressants
	Polio
	Chagas
	Infectious mononucleosis
Post-surgical	Human immunodeficiency virus
	Heller myotomy
Idiopathic	Peroral endoscopic myotomy
	-

with the underlying motility disorder [30]. One study showed that lansoprazole 30 mg was effective in controlling GERD symptoms among scleroderma patients for 6 months; however,

this benefit was not sustained after 6 months [31]. Muro *et al* studied the efficacy of rabeprazole 10 mg in scleroderma patients with GERD symptoms and EE, using a validated questionnaire (frequency scale for symptoms of GERD), and found that rabeprazole significantly reduced GERD symptom severity after 4 and 8 weeks of treatment [32]. Double-dose PPI is often used to control GERD symptoms and EE in clinical practice, although support for this is scarce in the medical literature [33-36].

Potassium-competitive acid blockers (P-CABs) work by inhibition of the gastric hydrogen potassium ATPase. The developing P-CAB class presently comprises fexuprazan, keverprazan, revaprazan, tegoprazan, and vonoprazan, while others are under development (i.e., linaprazan, zastaprazan). Vonoprazan is the most popular medication of P-CAB and the most studied so far [37]. Vonoprazan is an orally active P-CAB approved for the treatment of EE. Vonoprazan was effective and non-inferior to lansoprazole for curing EE [37]. In *post hoc* analyses, patients with severe esophagitis (LA Grades C or D) experienced better treatment effects in the vonoprazan group than in the lansoprazole group. Shirai *et al* investigated the efficacy of Vonoprazan for the treatment of PPI-refractory EE in 10 patients with systemic sclerosis [38]. The authors reported that switching patients to vonoprazan improved the endoscopic findings of reflux esophagitis and 6 patients achieved mucosal healing. Other clinical trials, mainly carried out in Asian countries, have shown non-inferiority of other P-CABs compared to PPI formulations for initial EE healing, including tegoprazan in Korean patients and keverprazan in Chinese patients [37].

Combination therapies have rarely been assessed in scleroderma GERD patients. A study by Foocharoen *et al*

Table 2 Percentage of patients with absent contractility (AC) who have an underlying rheumatologic disease

Author [ref.]	Year published	Location	Total number of AC patients	Number with a rheumatologic or autoimmune disease	Number with systemic sclerosis
Laique <i>et al</i> [4]	2019	Cleveland, USA	207	169 (81.6%)	132 (63.7%)
Kovacs <i>et al</i> [27]	2021	Phoenix, USA	59	22 (37.3%)	11 (18.6%)
Cohen <i>et al</i> [283]	2022	Israel	74	16 (21.6%)	5 (6.8%)
Dao <i>et al</i> [29]	2022	Vietnam	204	0 (0%)	0 (0%)
Alcala-Gonzalez <i>et al</i> [25]	2023	Barcelona, Spain	72	31 (43.1%)	22 (30.6%)
Ikebuchi <i>et al</i> [26]	2023	Japan	54	22 (40.7%)	18 (33.3%)

included 148 scleroderma patients with GERD who had only partial response to PPIs [39]. The authors compared the addition of domperidone or alginic acid to PPIs and concluded that this approach was effective in most cases. However, 20% of patients still did not show any kind of improvement [39]. Sucralfate, composed of sucrose sulfate and aluminum hydroxide, is often added as a complementary therapy to control reflux symptoms and EE. One meta-analysis that included GERD trials of patients with EE (43 articles, 7635 patients) reported that the overall healing rate with sucralfate was (39.2±22.4%, 95% confidence interval 3.6-74.8%) [40].

Esophageal peptic stricture formation is a significant complication of chronic GERD and can further aggravated dysphagia symptoms. The use of PPIs has reduced the incidence of esophageal strictures. When identified, peptic strictures can be treated with PPIs and endoscopic dilation [41].

In summary, GERD and EE are very common in patients with AC, and PPIs remain the cornerstone of treatment in these patients.

Prokinetics drugs in patients with AC

There is limited evidence regarding the use of prokinetic pharmacological treatment in patients with AC. Indeed, most of the current knowledge regarding the effectiveness of prokinetics in patients with esophageal disorders derives from studies conducted in patients with manometric patterns different from AC. Therefore, in this review, we are only speculating on their potential utility in AC. While prokinetics may provide some symptomatic relief in mild neurologic/myopathic impairments, in advanced stages of fibrosis (such as in AC patients), therapeutic agents are expected to be ineffective in improving esophageal motility [42,43].

Prokinetic agents represent a diverse group of medications that target neurotransmitters responsible of orchestrating smooth muscle contractility, comprising dopamine antagonists (metoclopramide, domperidone), serotonin agents (buspirone, prucalopride, mosapride) and motilin receptor agonists (erythromycin) [44]. As a group, prokinetics positively impact the lower esophageal sphincter (LES) pressures and esophageal peristalsis, increasing the amplitude of esophageal contractions. However, most of these pharmacological compounds are also characterized by a high risk of adverse events, which may be

serious, including cardiac arrest and extrapyramidal symptoms that may occur in some patients, particularly during prolonged treatments. Therefore, most available evidence derives from short-term clinical studies in a small number of patients, and the overall quality of evidence is poor.

In healthy volunteers, dopamine-2 receptor antagonists have been found to increase esophageal contractions (metoclopramide) and improve LES basal tone (domperidone and metoclopramide). Despite this, they failed to improve esophageal body motility in a randomized, double-blind, placebo-controlled study in patients with EE [45].

Serotonergic agents are another group of prokinetic drugs that could improve esophageal motility, by targeting either the presynaptic 5-HT_{1A} receptors (buspirone) or the post-synaptic 5HT-4 receptors (prucalopride, itopride and mosapride), ultimately leading to an increased release of acetylcholine from the enteric nerves and stimulating esophageal peristalsis via the activity on muscarinic receptors. Prucalopride may improve gastric emptying rates in healthy subjects and can increase peristalsis and reduce esophageal acid exposure times in GERD patients with hypomotility [46]. Finally, motilin agonists include erythromycin, a macrolide antibiotic able to activate motilin receptors on smooth muscle fibers. Following acute intravenous administration in diabetic patients with esophageal hypomotility, erythromycin was able to increase esophageal transit time, as assessed by esophagogastric scintigraphy, and to significantly improve esophageal contractions [47,48]. This drug, however, is associated with serious cardiac side effects (QT-interval prolongation) and is characterized by rapid tachyphylaxis, making it unfit for long-term symptom control.

In conclusion, prokinetic agents have mostly been tested for short periods of time and in a small number of patients with esophageal hypocontractility disorders. None of the pharmacological agents tested has resulted in improvements in terms of manometry parameters or upper gastrointestinal symptoms in AC patients over placebo (Table 3).

Prevalence and management of esophageal candidiasis in AC

In patients with AC, symptoms of dysphagia may be the result of esophageal candidiasis as well as of the dysmotility itself [13], which presents with features including dysphagia, odynophagia,

Table 3 Potential treatment options for esophageal absent contractility

Treatment options	
Prokinetic drugs	Metoclopramide Domperidone
Serotonin agents	Buspirone Prucalopride Mosapride Itopride
Motilin receptor agonists	Erythromycin
Nutritional management	Gastric route Jejunal route Parenteral route
Endoscopic	Peroral endoscopic myotomy
Surgical	Partial fundoplication
Electrical	Transcutaneous electrical stimulation

and pain behind the sternum [49]. *Candida albicans* is the most common cause of infectious esophagitis. It most commonly develops secondary to an immunocompromised state, but in nearly 25% of patients the underlying cause is esophageal stasis associated with achalasia, scleroderma or peptic strictures [50,51]. Studies have shown that approximately 10% of patients with esophageal candidiasis have an underlying esophageal motility disorder [52,53]. Additionally, in a study of patients with AC who had undergone esophagogastroduodenoscopy with biopsy, esophageal candidiasis was confirmed in 8.8% [27]. AC is a predisposing factor for esophageal candidiasis, as the stasis facilitates fungal colonization in the esophagus [50]. PPI use is also associated with esophageal candidiasis and may contribute to the development of candidiasis in AC patients. For example, Abdimajid *et al* reported that about 72% of HIV-negative patients with esophageal candidiasis used PPIs or other acid suppression drugs [49]. Conclusive diagnosis is via endoscopy, which reveals white mucosal plaque-like lesions that cannot be washed off with water from irrigation, along with biopsy or cytological/microbiologic evaluation [49].

The standard treatment for esophageal candidiasis is systemic antifungal therapy, most commonly oral fluconazole 200-400 mg for 14-21 days, or intravenous for patients unable to tolerate oral medication. Other treatment options include itraconazole or voriconazole. In non-responsive esophageal candidiasis, amphotericin B may be prescribed, but this has serious side-effects and therefore routine use should be avoided; posaconazole may be prescribed in refractory cases [49]. Use of intestinal flora regulators as well as B vitamins may also enhance the resistance of local tissues and inhibit candida growth [49]. There is no recommendation of topical antifungal treatment for esophageal candidiasis, although topical clotrimazole or nystatin is often used as first-line treatment of mild oropharyngeal candidiasis [54]. Prolonged esophageal candidiasis may lead to stricturing of the esophagus, especially in comorbid connective tissue disease [49]. In a 2002 study, esophageal candidiasis symptoms recurred in 17% of patients given fluconazole 4 weeks after stopping the study drug [55].

Nutritional management

Patients with esophageal dysmotility disorders may suffer from dysphagia, which makes the adequate intake of calories and protein challenging. The failure of macro- and micronutrients to reach the stomach may result in malnutrition [56]. Malnutrition is identified in 18-56% of patients with systemic sclerosis, most probably due to the intestinal rather than the esophageal dysmotility [55]. Nutritional support is important in improving outcomes for AC disorders and is especially crucial in children to maintain growth [56,57]. For patients who screen positive for nutritional deficiencies, it is recommended to refer them to a registered dietitian or nutritionist [56,58], who should construct a diet balancing fluids, protein, fat and carbohydrates based on the patient's age, weight and individual characteristics (such as the need for catch-up growth in children) [57].

In general, enteral nutrition is preferable to parenteral nutrition, as it preserves gut function, mucosal architecture, gut-associated lymphoid tissue and gut microbiota, as well as reducing the cost and length of stay, with fewer infectious complications [57]. If an oral diet is not tolerated, enteral nutrition should be provided via nasogastric feeding tube, which reduces the risk of aspiration [56]. Patients should be fed in an upright position and eating should be minimized for several hours before bedtime [57].

Gastric or jejunal feeding through percutaneous or surgically placed tubes should be employed when dysphagia precludes oral supplementation, or when enteral support is needed for more than 4-5 weeks [57,58]. In patients with severe gastrointestinal dysmotility or contraindications to enteral feedings, parenteral nutrition is an effective treatment for refractory malnutrition. Although there is minimal research on the outcomes of nutritional support in patients with AC, case reports have shown weight gain and subsequent improvement in quality of life [58]. In a study of the impact of nutritional status on patients with systemic sclerosis, patients who received a high-energy, high protein, oral liquid nutritional supplement for 12 weeks were observed to have improved hand grip strength and subjective global assessment [59] (Table 3).

Endoscopic, surgical, and transcutaneous management

Patients with AC often present with reflux symptoms or dysphagia [28,60]. A recent study showed that patients who present with reflux symptoms tended to have a lower integrated relaxation pressure (IRP) on HRM, suggesting that this plays a role in facilitating the reflux of gastric content into the esophagus [60]. On the other hand, dysphagia-predominant patients tended to have a higher IRP (although still within the normal limit), suggesting that this leads to food sticking at the esophagogastric junction. These differences in IRP also suggest that interventions to the esophagogastric junction, such as a myotomy in patients with dysphagia and a relatively high IRP,

or a fundoplication in patients with reflux and a low IRP, may have a physiological basis to be considered in patients with AC [60].

Currently, the treatment for AC is mainly medical management, including a wide variety of medications, as described above. While surgical and endoscopic treatment approaches for AC are not well-established, several case series have showed that fundoplication, mainly via the partial approach, is feasible in GERD patients with AC and does not lead to significant dysphagia [61-63]. Moreover, a recent prospective study published by Tran *et al* reported that laparoscopic anterior partial fundoplication was shown to be effective in the treatment of GERD symptoms in 40 patients with AC over a 10-year follow-up period. Additionally, there was no increase in dysphagia at 5- and 10-year follow-ups post-surgery [64].

Regarding endoscopic management, the data are scarce, as only 1 previous study reported on performing POEM in 6 patients with AC who suffered from dysphagia. This small case series showed symptom improvement after POEM, as assessed by the Eckardt score. However, there was less post-POEM symptom improvement in AC patients compared to patients with achalasia or esophagogastric junction outflow obstruction [65]. Thus, there are currently insufficient data to recommend POEM in dysphagia-predominant AC patients. Such patients often require further evaluation to assess whether they actually have type 1 achalasia as their underlying motility disorder.

Finally, a recently published study on the yield of acute transcutaneous electrical stimulation (TES) has reported TES-induced measurable contractile activity (Distal Contractile Integral [DCI] >100 mmHg-cm-sec) in 3 out of 5 patients with AC: median DCI (interquartile range) 0 (0) mmHg-cm-s off TES vs. 0 (182) mmHg-cm-s on TES; $P < 0.001$ [66] (Table 3).

Concluding remarks

Recent studies have given us a better understanding of AC, an often-overlooked esophageal motility disorder. These studies have improved our knowledge of the clinical presentation of AC and its relationship with rheumatologic diseases. However, there remains a lack of quality evidence regarding treatment options. The mainstay of treatment continues to be aggressive use of PPIs for reflux symptoms and EE, as well nutritional support and lifestyle modification. Other medications, such as prokinetic agents, currently have little evidence to support their use. There are limited studies evaluating interventions such as fundoplication to treat reflux in patients with AC. Further prospective clinical studies evaluating these therapeutic options, as well as novel treatments, are certainly warranted.

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